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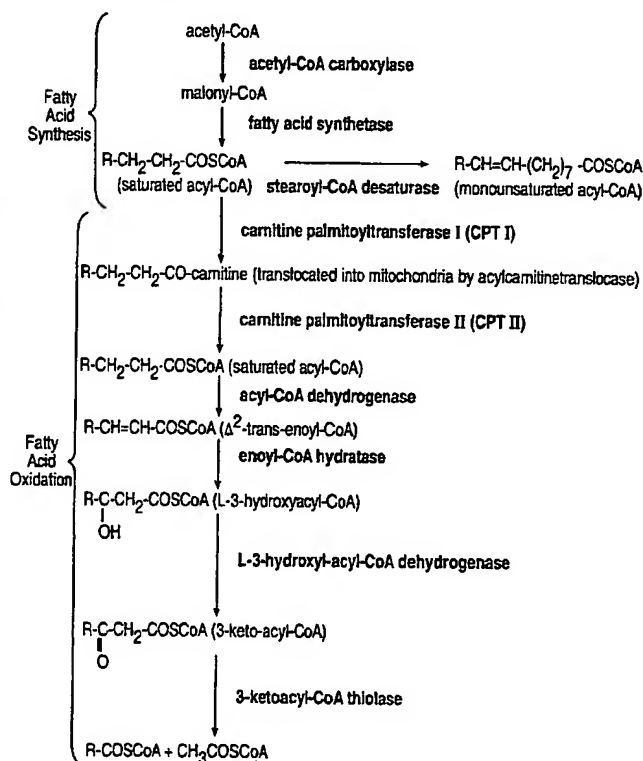
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(54) Title: REDUCTION OF HAIR GROWTH

Fatty acid metabolism pathway



(57) Abstract: Mammalian hair growth can be reduced by topical application of an inhibitor of fatty acid metabolism.

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REDUCTION OF HAIR GROWTH

The invention relates to reducing hair growth in mammals, particularly for cosmetic purposes.

A main function of mammalian hair is to provide environmental
5 protection. However, that function has largely been lost in humans, in whom hair is kept or removed from various parts of the body essentially for cosmetic reasons. For example, it is generally preferred to have hair on the scalp but not on the face.

Various procedures have been employed to remove unwanted hair,
including shaving, electrolysis, depilatory creams or lotions, waxing, plucking, and
10 therapeutic antiandrogens. These conventional procedures generally have drawbacks associated with them. Shaving, for instance, can cause nicks and cuts, and can leave a perception of an increase in the rate of hair regrowth. Shaving also can leave an undesirable stubble. Electrolysis, on the other hand, can keep a treated area free of hair for prolonged periods of time, but can be expensive, painful, and sometimes leaves
15 scarring. Depilatory creams, though very effective, typically are not recommended for frequent use due to their high irritancy potential. Waxing and plucking can cause pain, discomfort, and poor removal of short hair. Finally, antiandrogens -- which have been used to treat female hirsutism -- can have unwanted side effects.

It has previously been disclosed that the rate and character of hair growth
20 can be altered by applying to the skin inhibitors of certain enzymes. These inhibitors include inhibitors of 5-alpha reductase (see, for example, Breuer et al., U.S. Pat. No. 4,885,289); ornithine decarboxylase (see, for example, Shander, U.S. Pat. No. 4,720,489), S-adenosylmethionine decarboxylase (see, for example Shander, U.S. patent 5,132,293); adenylosuccinate synthase (see, for example, Ahluwalia); U.S. Pat. No. 5,095,007);
25 aspartate transcarbamylase (see, for example, Ahluwalia, U.S. Pat. No. 5,095,007); gamma-glutamyl transpeptidase (see, for example, Ahluwalia et al., U.S. Pat. No. 5,096,911); transglutaminase (see, for example, Shander, et al., U.S. Patent 5,143,925); L-asparagine synthetase (see, for example, Ahluwalia, U.S. Patent 5,444,090); 5-lipoxygenase (see, for example, Ahluwalia et al., U.S. Patent 6,239,170); cyclooxygenase
30 (see, for example, Ahluwalia et al., U.S. Patent 6,248,751); nitric oxide synthase (see, for example Ahluwalia et al., U.S. Patent 5,468,476); ornithine aminotransferase (see, for example, Shander et al., U.S. Patent 5,474,763); cysteine synthetic pathway enzymes including L-methionine S-adenosyltransferase. L-homocysteine S-methyl transferase, S-

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adenosyl homocysteine hydrolyase, cystathionine synthase and cystathionase (see, for example, Ahluwalia et al., U.S. Patent 5,455,234); cholesterol synthesis pathway enzymes including HMGCoA reductase and squalene synthetase (see, for example, Henry et al., U.S. Patent 5,840,752); protein kinase C (see, for example, Ahluwalia et al., U.S. Patent 5,554,608); arginase (see, for example, Shander et al., U.S. Patent 5,728,736); matrix metalloproteinase (see for example Styczynski et al., U.S. Patent 5,962,466); DNA topoisomerase (see, for example Styczynski et al., U.S. Patent 6,037,326); aminoacyl-tRNA synthetase (see, for example, Henry et al., U.S. Patent 5,939,458); hypusine biosynthetic pathway enzymes including deoxyhypusine synthase and deoxyhypusine hydroxylase (see, for example, Styczynski et al. U.S. Patent 6,060,471); alkaline phosphatase (see, for example Styczynski et al., U.S. Patent 6,020,006); and protein-tyrosine kinase (see, for example Henry et al., U.S. Patent 6,121,269).

U.S. Patent 5,908,867 (Henry et al.) describes a method for reducing mammalian hair growth by inhibiting the formation of glycoproteins, proteoglycans or glycosaminoglycans, for example by use of inhibitors of the synthesis of N-acetyl glucosamine-pyrophosphoryl-dolichyl, chondroitin sulfate, keratin sulfate, dermatan sulfate, heparan sulfate, heparin, hyaluronic acid, inhibitors of the formation of Glc₃Man₉-(GlcNAc)₂-PP-dolichol or glycosaminoglycan hyaluronic acid, inhibitors of the transfer of Glc₃Man₉-(GlcNAc)₂, inhibitors of the enzymes glucosidase I, glucosidase II, mannosidase I, mannosidase II, and β-galactosidase and compounds that affect the exocytosis of proteoglycans.

U.S. Patents 5,652,273, 5,824,665 and 6,218,435 (all issued to Henry et al.) describe ways of reducing mammalian hair growth by suppression of the metabolic pathway for conversion of glucose to acetyl-Co-A. This can be effected by, inter alia, inhibition of hexokinase, phosphofructokinase, aldolase, phosphoglycerate kinase, enolase, pyruvate kinase or pyruvate dehydrogenase or by an inhibitor of glucose transport.

Other methods for modulating hair growth include use of compounds that induce or activates conjugation of an androgen, for example as described by Styczynski et al., in U.S. Patent 5,958,946; use of compounds to increase cellular ceramide levels for example as described by Styczynski et al., in U.S. Patent 6,235,737; use of non-steroidal suppressors of angiogenesis, for example as described in Ahluwalia in U.S. Patent

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6,093,748; use of catechin compounds, for example as described in U.S. Patents 5,674,477 and 5,776,442 (Ahluwalia); use of sulfhydryl reactive compounds for example as described in Shander et al. In U.S. Patent 5,411,991; and use of pantothenic acid or an analogue thereof, for example as described by Ahluwalia et al in U.S. Patent 5,364,885.

5 Fatty acids can regulate biological functions by providing metabolic fuel and/or being a part of the structural components of cellular membranes. The extent of this regulation depends on the tissue. In mammalian cells fatty acid metabolism generally includes the fatty acid synthesis and fatty acid oxidation. The fatty acid synthesis occurs in cell cytosol and produces long-chain fatty acids for various cellular functions. The
10 oxidation pathway occurs in the cellular compartment mitochondria and generates energy to support various cellular processes.

The fatty acid oxidation is a metabolic process under which ATP is formed by oxidative phosphorylation. In heart and skeletal muscle, fatty acid oxidation provides the major source of energy under a variety of conditions. For example, during
15 prolonged fasting and starvation, fatty acid oxidation provides acetyl-CoA for the synthesis of "ketone bodies" that are used as an alternate fuel in some tissues, such as brain, when the supply of glucose is low.

Long-chain fatty acids such as palmitic acid and stearic acid are major substrates for fatty acid oxidation. The pathway for the fatty acid oxidation is
20 summarized in the Figure. In mammalian cells, free fatty acids are converted to CoA thioesters catalyzed by acyl-CoA synthetase. Because the inner mitochondrial membrane is a barrier to acyl-CoA, fatty acyl residues are carried across this membrane as carnitine esters. Carnitine palmitoyltransferase I (CPT I), which is located at the outer mito-
chondrial membrane, transfers fatty acid acyl residues from CoA to L-carnitine. The
25 resultant fatty acyl carnitines pass through the inner mitochondrial membrane via carnitine:acylcarnitine translocase. Once in the matrix, carnitine palmitoyltransferase II (CPT II) catalyzes the transfer of fatty acyl residues back from carnitine to CoA-SH. Acyl-CoA, formed in the matrix, is the substrate for fatty acid oxidation cycle that yields acetyl-CoA, NADH and FADH₂. The latter two compounds are oxidized by the
30 mitochondrial electron transport chain and acetyl-CoA is oxidized to CO₂ by tricarboxylic acid cycle. Hence, the complete oxidation of a long-chain fatty acid can produce several ATP molecules, which are utilized for energy-requiring cellular processes. The enzymes catalyzing the repetitive reactions of the fatty acid oxidation

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cycle include acyl-CoA dehydrogenase, enoyl-CoA hydratase, L-3-hydroxyacyl-CoA dehydrogenase and 3-ketoacyl-CoA thiolase.

Long-chain fatty acids are not only metabolic fuel for certain tissues but are also structural components of cellular membranes. Most long-chain fatty acids are derived from either diet or *de novo* synthesis. Fatty acid synthesis, which produces long-chain fatty acids from acetyl-CoA, is mainly carried out in liver and adipose tissue. The synthesized fatty acids are converted to triacylglycerols, phospholipids and sphingolipids. Most triacylglycerols are stored in adipose tissues as energy source for other tissues such as skeletal muscle. Phospholipids and sphingolipids end up as constituents of cellular membrane.

The majority of long-chain fatty acids synthesized in mammalian cell are saturated fatty acids (e.g. palmitic acid) and monounsaturated fatty acids (e.g., oleic acid). Two major steps carry out the biosynthesis of saturated fatty acids from acetyl-CoA. The first step is the conversion of acetyl-CoA to malonyl-CoA, a reaction catalyzed by acetyl-CoA carboxylase. It is a rate-limiting step in the biosynthesis of fatty acids. The second step is the conversion of acetyl-CoA and malonyl-CoA to long-chain fatty acids, catalyzed by fatty acid synthetase in the presence of NADPH. Mammalian fatty acid synthetase are multifunctional proteins typically consisting of two identical subunits. The reaction starts from acetyl-CoA and malonyl-CoA and involves sequential reactions and acyl intermediates. Six more malonyl groups react successively at the carboxyl end of the growing fatty acid chain to form the end product palmitic acid.

Several inhibitors of acetyl-CoA carboxylase and fatty acid synthetase have been developed and used to inhibit fatty acid synthesis in various tissues. Among these, 5-(tetradecyloxy)-2-furoic acid (TOFA) and cerulenin have been commonly used to inhibit fatty acid synthesis both in vivo and in vitro. It has been shown that TOFA is converted to its CoA ester by isolated hepatocytes and the resulting compound 5-(tetradecyloxy)-2-furoyl-CoA is an effective inhibitor of acetyl-CoA carboxylase. Cerulenin can bind one of the functional domains of fatty acid synthetase and inhibit its activity.

Palmitoleic and oleic acids are major monounsaturated fatty acids in animal tissues. Palmitic and stearic acid serve as precursors to their synthesis. A *cis* double bond is introduced in the Δ^9 position (between carbons 9 and 10) of these molecules by the stearoyl-CoA desaturase complex to form the respective

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monounsaturated fatty acid. The desaturase complex is located in the endoplasmic reticulum and consists of three proteins (i) cytochrome b₅ reductase, (ii) cytochrome b₅ and (iii) the desaturase. During desaturation, the electrons flow sequentially from NAD(P)H, through cytochrome b₅ reductase, to cytochrome b₅, to the stearyl-CoA desaturase, and finally to active oxygen which is reduced to H₂O.

BRIEF DESCRIPTION OF THE DRAWINGS

The Figure is a general summary of fatty acid metabolism.

In one aspect, the invention provides a method (typically a cosmetic method) of reducing unwanted mammalian (preferably human) hair growth by applying to the skin a compound that inhibits fatty acid metabolism in an amount effective to reduce hair growth. The unwanted hair growth may be undesirable from a cosmetic standpoint or may result, for example, from a disease or an abnormal condition (e.g., hirsutism). The compound may be, for example, an inhibitor of an enzyme involved in fatty acid oxidation or fatty acid synthesis.

Typically, in practicing the aforementioned method, the compound will be included in a topical composition along with a dermatologically or cosmetically acceptable vehicle. Accordingly, the present invention also relates to topical compositions comprising a dermatologically or cosmetically acceptable vehicle and a compound that inhibits fatty acid metabolism in an amount effective to reduce hair growth.

In addition, the present invention relates to the use of a compound that inhibits fatty acid metabolism for the manufacture of a therapeutic topical composition for reducing hair growth.

Other features and advantages of the invention may be apparent from the description of the preferred embodiments thereof, and from the claims.

An example of a preferred composition includes at least one inhibitor of an enzyme involved in fatty acid oxidation or fatty acid synthesis in a cosmetically and/or dermatologically acceptable vehicle. The composition may be a solid, semi-solid, or liquid. The composition may be, for example, a cosmetic and dermatologic product in the form of an, for example, ointment, lotion, foam, cream, gel, or solution. The composition may also be in the form of a shaving preparation or an aftershave.

Examples of inhibitors of carnitine palmitoyltransferase I (CPT I) include adriamycin; D,L-aminocarnitine; acylamino carnitines; decanoylcarnitine; amiodarone;

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2-bromopalmitic acid; 2-bromopalmitoylcarnitine; 2-bromopalmitoyl-CoA; 2-bromomyristoylthiocarnitine; emeriamine; erucic acid; erucylcarnitine; etomoxir; etomoxiryl-CoA; glyburide; hemiacetylcarnitinium chloride; hemipalmitoylcarnitinium chloride; 3-hydroxy-5,5-dimethylhexanoic acid (HDFH); methyl palmoxirate (methyl-tetradecylglycidate); 2-tetradecylglycidic acid; oxfenicine; perhexiline; 2[5(4-chlorophenyl) pentyl]-oxirane-2-carboxylic acid (POCA); 2-[3-(3-trifluoromethylphenyl)-propyl]oxiran-2-carbonyl-CoA; 2-[5-(4-chlorophenyl)pentyl]-oxiran-2-carbonyl-CoA; 2-(5-phenylpentyl)oxiran-2-carbonyl-CoA; 2-tetradecyloxiran-2-carbonyl-CoA; 8,N,N-diethylamino-octyl-3,4,5-trimethoxybenzoate (TMB-8); tolbutamide; and trimetazidine.

Examples of inhibitors of acyl-CoA dehydrogenase include hypoglycin; 2-mercaptoacetic acid; 3-mercaptopropionic acid; methylenecyclopropylacetic acid (MCPA); methylenecyclopropylformic acid (C₆MCPA); spiropentaneacetic acid; 3-methyleneoctanoyl-CoA; and 3-methyl-trans-2-octenoyl-CoA.

Examples of inhibitors of 3-ketoacyl-CoA thiolase include 4-bromocrotonic acid; 2-bromooctanoic acid; 2-bromo-3-ketooctanoyl-CoA; 4-bromo-2-octenoic acid and 4-pentenoic acid.

Examples of inhibitors of acetyl-CoA carboxylase include 5-(tetradecyloxy)-2-furoic acid (TOFA); sethoxydim (cyclohexanedione); medica 16 (β,β' -methyl-substituted hexadecanedioic acid); 2-n-pentadecyl-benzimidazole-5-carboxylate; and 2-methyl-2-(p-(1,2,3,4-tetrahydro-naphthyl)phenoxy)propionic acid (TPLA).

Examples of inhibitors of fatty acid synthetase include cerulenin; carbacerulenin; and 3-carboxy-4-alkyl-2-methylenebutyrolactone (C75).

An example of an inhibitor of stearoyl-CoA desaturase is sterculic acid. The inhibitors just mentioned are known.

The composition may include more than one inhibitor of an enzyme involved in fatty acid oxidation or fatty acid synthesis. In addition, the composition may include one or more other types of hair growth reducing agents, such as those described in U.S. Pat. No. 4,885,289; U.S. Pat. No. 4,720,489; U.S. Pat. No. 5,132,293; U.S. Pat. 5,096,911; U.S. Pat. No. 5,095,007; U.S. Pat. No. 5,143,925; U.S. Pat. No. 5,328,686; U.S. Pat. No. 5,440,090; U.S. Pat. No. 5,364,885; U.S. Pat. No. 5,411,991; U.S. Pat. No. 5,648,394; U.S. Pat. No. 5,468,476; U.S. Pat. No. 5,475,763; U.S. Pat. No. 5,554,608; U.S. Pat. No. 5,674,477; U.S. Pat. No. 5,728,736; U.S. Pat. 5,652,273; WO 94/27586; WO 94/27563; and WO 98/03149, all of which are incorporated herein by reference.

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The concentration of the inhibitor in the composition may be varied over a wide range up to a saturated solution, preferably from 0.1% to 30% by weight or even more; the reduction of hair growth increases as the amount of inhibitor applied increases per unit area of skin. The maximum amount effectively applied is limited only by the rate at which the inhibitor penetrates the skin. The effective amounts may range, for example, from 10 to 3000 micrograms or more per square centimeter of skin.

The vehicle can be inert or can possess cosmetic, physiological and/or pharmaceutical benefits of its own. Vehicles can be formulated with liquid or solid emollients, solvents, thickeners, humectants and/or powders. Emollients include stearyl alcohol, mink oil, cetyl alcohol, oleyl alcohol, isopropyl laurate, polyethylene glycol, petroleum jelly, and myristyl myristate. Solvents include ethyl alcohol, isopropanol, acetone, diethylene glycol, ethylene glycol, dimethyl sulfoxide, and dimethyl formamide.

The composition also can include components that enhance the penetration of the inhibitor into the skin and/or to the site of action. Examples of penetration enhancers include urea, polyoxyethylene ethers (e.g., Brij-30 and Laureth-4), 3-hydroxy-3,7,11-trimethyl-1,6,10-dodecatriene, terpenes, cis-fatty acids (e.g., oleic acid, palmitoleic acid), acetone, laurocapram, dimethylsulfoxide, 2-pyrrolidone, oleyl alcohol, glyceryl-3-stearate, propan-2-ol, myristic acid isopropyl ester, cholesterol, and propylene glycol. A penetration enhancer can be added, for example, at concentrations of 0.1% to 20% or 0.5% to 5% by weight.

The composition also can be formulated to provide a reservoir within or on the surface of the skin to provide for a continual slow release of the inhibitor. The composition also may be formulated to evaporate slowly from the skin, allowing the inhibitor extra time to penetrate the skin.

Example 1

A composition prepared containing 10% by weight of palmitoyl DL carnitine in a vehicle containing 68% water, 16% ethanol, 5% propylene glycol, 5% dipropylene glycol, 4% benzyl alcohol and 2% propylene carbonate.

Example 2

A composition prepared containing 10% by weight of amiodarone in a vehicle containing 68% water, 16% ethanol, 5% propylene glycol, 5% dipropylene glycol, 4% benzyl alcohol and 2% propylene carbonate.

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Example 3

A composition prepared containing 10% by weight of DL-decanoylcarnitine chloride in a vehicle containing 80% ethanol, 17.5% water, 2% propylene glycol dipelargonate (Emerest 2388), and 0.5% propylene glycol.

5

Example 4

A composition prepared containing 2.5% by weight of perhexiline in a vehicle containing 80% ethanol, 17.5% water, 2% propylene glycol dipelargonate (Emerest 2388), and 0.5% propylene glycol.

Example 5

10 A composition prepared containing 10% by weight of glynbenclamide in a vehicle containing 70% ethanol, 30% propylene glycol.

Example 6

A composition prepared containing 10% by weight of 4-tert-butylbenzoic acid in a vehicle containing 64% ethanol, 20% dimethyl sulfoxide 14% water, 1.6% propylene glycol dipelargonate (Emerest 2388), and 0.4% propylene glycol.

15

Example 7

A composition prepared containing 10% by weight of 4-pentenoic acid in a vehicle containing 68% water, 16% ethanol, 5% propylene glycol, 5% dipropylene glycol, 4% benzyl alcohol and 2% propylene carbonate.

20

Example 8

A composition prepared containing 2% by weight of methyl palmoxirate in a vehicle containing 80% ethanol, 17.5% water, 2% propylene glycol dipelargonate (Emerest 2388), and 0.5% propylene glycol.

Example 9

25 A composition prepared containing 3% by weight of 4-bromocrotonic acid in a vehicle containing 80% ethanol, 17.5% water, 2% propylene glycol dipelargonate (Emerest 2388), and 0.5% propylene glycol.

Example 10

30 A composition containing an inhibitor of carnitine palmitoyl transferase-I at a dose of 1 - 10% by weight in a cream based vehicle containing water 80.84%, glyceryl stearate 4.24%, polyethylene glycol 100-stearate 4.09%, cetearyl alcohol 3.05%, cetareth-20 2.5%, mineral oil 2.22%, stearyl alcohol 1.67%, dimethicone 0.56%.

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Example 11

Any one or more of the previous examples in combination with one or more of the penetration enhancers selected from urea, propan-2-ol, polyoxyethylene ethers, terpenes, cis-fatty acids (oleic acid, palmitoleic acid), acetone, laurocapram, 5 dimethylsulfoxide, 2-pyrrolidone, oleyl alcohol, glyceryl-3-stearate, cholesterol, myristic acid isopropyl ester, propylene glycol.

The composition should be topically applied to a selected area of the body from which it is described to reduce hair growth. For example, the composition can be applied to the face, particularly to the beard area of the face, i.e., the cheek, neck, upper 10 lip, and chin. The composition also may be used as an adjunct to other methods of hair removal including shaving, waxing, mechanical epilation, chemical depilation, electrolysis and laser-assisted hair removal.

The composition can also be applied to the legs, arms, torso or armpits. The composition is particularly suitable for reducing the growth of unwanted hair in 15 women having hirsutism or other conditions. In humans, the composition should be applied once or twice a day, or even more frequently, to achieve a perceived reduction in hair growth. Perception of reduced hair growth could occur as early as 24 hours or 48 hours (for instance, between normal shaving intervals) following use or could take up to, for example, three months. Reduction in hair growth is demonstrated when, for example, 20 the rate of hair growth is slowed, the need for removal is reduced, the subject perceives less hair on the treated site, or quantitatively, when the weight of hair removed (i.e., hair mass) is reduced.

Golden Syrian Hamster Assay

Male intact Golden Syrian hamsters are considered acceptable models for 25 human beard hair growth in that they display oval shaped flank organs, one on each side, each about 8 mm. in major diameter. These organs produce fine light colored hair typical of the animal pelage found on the body. In response to androgens the flank organs produce dark coarse hair similar to male human beard hair. To evaluate the effectiveness of a composition in reducing hair growth, the flank organs of each of a group of hamsters 30 are depilated by applying a thioglycolate based chemical depilatory (Surgex) and/or shaved. To one organ of each animal 10 μ l. of vehicle alone once a day is applied, while to the other organ of each animal an equal amount of vehicle containing the compound under evaluation is applied. After three weeks of topical applications (one application

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per day for five days a week), the flank organs are shaved and the amount of recovered hair (hair mass) from each is weighed. Percent-reduction of hair growth is calculated by subtracting the hair mass (mg) value of the test compound treated side from the hair mass value of the vehicle treated side; the delta value obtained is then divided by the hair mass value of the vehicle treated side, and the resultant number is multiplied by 100.

The above-described assay will be referred to herein as the "Golden Syrian hamster" assay or "hair mass" assay. Preferred compositions provide a reduction in hair growth of at least about 15% and more preferably at least about 35%, when tested in the Golden Syrian hamster assay.

10 Human Hair Follicle Growth Assay

Tissue source - Human skin was obtained from a plastic surgeon as a by-product of face-lift procedures. Immediately after removal, the skin was placed in Williams E medium containing antibiotics and refrigerated. The Williams E medium is a commercially obtained medium which has been formulated with essential nutrients for maintaining viability of tissues or cells such as of hair follicle in an in-vitro environment.

Hair Follicle Isolation and Culture - Human hair follicles in growth phase (anagen) were isolated from face-lift tissue under a dissecting scope using a scalpel and watchmakers forceps. The skin was sliced into thin strips exposing 2 - 3 rows of follicles that could readily be dissected. Follicles were placed into 0.5 ml Williams E medium supplemented with 2 mM L-glutamine, 10 µg/ml insulin, 100 ng/ml hydrocortisone, 100 units penicillin, 0.1 mg/ml streptomycin and 0.25 µg/ml amphotericin B. The follicles were incubated in 24 well plates (1 follicle/well) at 37°C in an atmosphere of 5% CO₂ and 95% air. Hair follicles were video recorded in the 24-well plates under the dissecting scope under a power of 10X. Typically, hair follicle lengths were measured on day 0 (day follicles were placed in culture) and again on day 7. When testing compounds, the compound was included in the culture medium from time 0 and remained in the medium throughout the course of the experiment. The length of hair follicles was assessed using an image analysis software system (Jasc Image Robot).

Assay of carnitine palmitoyl transferase-I (CPT-I)

30 Two different enzyme assays were used to quantify the activity of CPT-I in hair follicles:

Method-I

Hair follicle rich fraction from hamster flank organs are homogenized in

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Buffer A (200mM mannitol, 10mM sucrose, 5mM MOPS pH 7.4). The homogenate is centrifuged at 2000 rpm for 10 minutes. The supernatant is removed and centrifuged at 7000 rpm for 30 minutes. The pellet is resuspended in Buffer B (20mM Tris-HCl, pH 7.4), 400 mM sucrose, 80 mM KCl, 2 mM EDTA, 2.6 mg/ml fatty acid free BSA). 30 μ l of the resuspended pellet is added to 35 μ l of DMSO or one of the inhibitors diluted in DMSO so that the final concentration is 5mM. After a 15 min preincubation, the following are added; 35 μ l of 1.7 mM palmitoyl Co-A (34% water and 66% Buffer B), 10 μ l of 5 mM L-carnitine (in buffer B with 0.5 μ Ci 3 H-carnitine). The reaction is then placed in a 37°C water bath for 30 minutes. At the end of 30 minutes the reaction is stopped by the addition of 150 μ l cold 1N HCl. This is followed by the addition of 250 μ l water to each sample. Butanol (500 μ l) is then added to each sample and the samples are centrifuged for 2 minutes at 10,000xg. 300 μ l of the butanol layer is transferred to a new centrifuge tube and 250 μ l of water is added. 200 μ l of the organic phase is added to a scintillation vial containing 12 ml of scintillation cocktail. The radioactivity is determined using a scintillation counter.

Method II

The enzyme activity of carnitine palmitoyl transferase-I (CPT-I) was also determined in the isolated mitochondrial fraction. Isolation of mitochondria from the hair follicle rich fraction of flank organs was accomplished by conventional differential centrifugation in 0.25 M sucrose, 10 mM Tris-HCl, pH 7.4 and 1 mM EDTA after tissues were homogenized by polytron homogenizer and Dounce tissue grinder. The pellet obtained at 7000 g was washed two times and finally suspended at 40-80 mg/ml. Carnitine palmitoyltransferase was measured as the rate of conversion of palmitoyl-CoA and [3 H]CH₃-L-carnitine into palmitoyl-[3 H]CH₃-l-carnitine. The incubation mixture initially contained 12.5 μ mol of Tris-HCl (pH 7.2), 15 μ mol of KCl, 3.1 μ mol of KCN, 6.2 μ mol of glutathione, 15 nmol of CoA, 2 mmol of MgSO₄, 2 μ mol of ATP (pH 6.8) in volume of 0.425 ml. To this mixture 50 μ l of mitochondria were added, followed by preincubation at 37° C for 10 minutes in the presence or absence of the enzyme inhibitor methyl palmoxirate (dissolved in DMSO). After preincubation, the enzyme reaction was initiated by the addition of 25 μ l of 2 mM palmitoyl-CoA and 25 μ l of 4 mM [3 H]CH₃-L-carnitine. The reaction was stopped after 30 minutes with 1 ml 1N HCl and palmitoyl-[3 H]CH₃-L-carnitine was extracted into n-butanol. The radioactivity was determined using scintillation spectrometry.

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Assay of 3-ketoacyl-CoA thiolase

Mitochondria were isolated as described in previous section (D) and preincubated with 100 μ M 4-bromocrotonic acid for 5 min. Aliquots of the mitochondrial suspension (50 μ l) were rapidly frozen in dry ice and stored at -80°C until
5 enzyme activities were assayed as described below. To insure the complete disruption of mitochondria, Triton X-100 (0.06%) was added to all assay mixtures. The activity of thiolase was determined by spectrophotometrically following the disappearance of the Mg^{2+} -enolate complex at 303 nm. The enzyme assay was performed at 25°C . The reaction mixture contained 0.1 M Tris-HCl (pH 8.2), 25 mM MgCl_2 , 30 mM KCl, 0.06%
10 Triton X-100, bovine serum albumin (0.13 mg/ml), 70 μ M CoA and 33 μ M acetoacetyl-CoA. Molar extinction coefficient of $21,400\text{ cm}^{-1}\text{M}^{-1}$ was used to calculate the rates determined with acetoacetyl-CoA.

Assay of acyl-CoA dehydrogenase

Mitochondria were isolated as described previously and preincubated with
15 1 mM methylenecyclopropylacetic acid (MCPA) for 5 min. Mitochondria were diluted to 1 mg/ml in 0.1% cholic acid and 50 mM phosphate buffer, pH 7.4. Acyl-CoA dehydrogenase activity was determined in a reaction medium containing 34 mM potassium phosphate (pH 7.2), 0.15 mM cytochrome c, 3.75 μ M rotenone, 200 μ M octanoyl-CoA and 3 mM phenazine ethosulfate. The assay was carried out at 37°C in a
20 final volume of 0.5 ml. Octanoyl-CoA was used as a substrate and converted to 2-enol-CoA by acyl-CoA dehydrogenase. The electron generated from the reaction was transferred to cytochrome c. The absorbance of reduced cytochrome c was monitored at 550 nm. Molar extinction coefficient of $19\text{ cm}^{-1}\text{mM}^{-1}$ was used to calculate the rate of reduced cytochrome c formation.

Results

25 The hair growth inhibitory efficacy of inhibitors of enzymes involved in fatty acid oxidation was evaluated in the Golden Syrian Hamster assay. Inhibitors of carnitine palmitoyltransferase I (CPT I), acyl-CoA dehydrogenase, and 3-ketoacyl-CoA thiolase were evaluated in this assay. The data indicate that inhibition of fatty acid
30 oxidation causes reduction of hair growth (Table I). A representative inhibitor for each enzyme also was evaluated in human hair follicle growth assay. The data show human hair growth inhibition by these compounds in this in-vitro model (Table II). In addition, cellular mitochondrial fraction of hamster flank organs hair follicles was isolated, and the

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enzyme activities of CPT I, acyl-CoA dehydrogenase and 3-ketoacyl-thiolase were measured in the presence and absence of select inhibitors. The results (Tables III, IV, V and VI) indicate that the activity of each enzyme can be detected in the mitochondrial fraction of hamster flank organ, and that the inhibitors reduce the activity of each enzyme. Taken together, the data indicate that the inhibition of enzymes involved in fatty acid oxidation results in a reduction of hair growth.

Inhibitors of two major fatty acid synthesis pathways, saturated fatty acid synthesis and monounsaturated fatty acid synthesis, also were tested in human hair follicle growth assay and/or the hamster hair mass assay. The data from these studies indicate that cerulenin, an inhibitor of fatty acid synthetase, can inhibit human hair follicle growth in vitro with marked efficacy (Table VII). The data also indicate that methyl sterulate, an inhibitor of stearoyl-CoA desaturase, can reduce hair growth both in vivo and in vitro as shown (Table VIII and IX).

TABLE I**Inhibition of hamster hair mass by inhibitors of fatty acid oxidation**

Compound	Dose (%)	Vehicle	Treated (mg)	Control (mg)	% Inhibition
palmitoyl DL carnitine	10.0	A*	0.29 ± 0.1	1.29 ± 0.17	73 ± 15
DL-decanoylcarnitine chloride	10.0	B*	0.94 ± 0.12	2.27 ± 0.21	58 ± 5
amiodarone	7.5	A*	1.62 ± 0.9	2.98 ± 0.62	44 ± 28
4-tert-butylbenzoic acid	10.0	C*	1.10 ± 0.12	2.14 ± 0.14	46 ± 8
glynbenclamide	10.0	D*	1.40 ± 0.32	1.96 ± 0.31	32 ± 8
perhexiline	2.5	B*	2.28 ± 0.77	3.06 ± 0.87	23 ± 25
4-pentenoic acid	10.0	A*	1.10 ± 0.12	2.14 ± 0.14	46 ± 8
methyl palmoxirate	2.0	B*	0.56 ± 0.12	1.70 ± 0.32	66 ± 4
4-bromocrotonic acid	3.0	B*	1.25 ± 0.37	1.86 ± 0.31	37 ± 14
2-propylpentanoic acid	20.0	A*	2.68 ± 0.20	0.87 ± 0.08	67 ± 3
methylenecyclopropyl-acetic acid (MCPA)	5.0	B*	2.3 ± 0.26	2.76 ± 0.2	16 ± 7

- *Vehicles: A -- 68% water, 16% ethanol, 5% propylene glycol, 5% dipropylene glycol, 4% benzyl alcohol and 2% propylene carbonate.
 B -- 80% ethanol, 17.5% water, 2% propylene glycol dipelargonate (Emerest 2388), and 0.5% propylene glycol.
 C -- 64% ethanol, 20% dimethyl sulfoxide 14% water, 1.6% propylene glycol dipelargonate (Emerest 2388), and 0.4% propylene glycol.
 D -- 70% ethanol, 30% propylene glycol.

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TABLE IIInhibition on human hair follicle growth by inhibitors of fatty acid oxidation

Inhibitor	Dose (mM)	Hair follicle length increase (mm)	% Inhibition
control (for methyl palmoxirate)	---	1.26 ± 0.65	0.00
5 methyl palmoxirate	0.1	0.54 ± 0.3	57 ± 24
control (for MCPA)	---	1.80 ± 0.50	0.00
methylenecyclopropyl-acetic acid (MCPA)	0.5	1.21 ± 0.26	33 ± 14
control (for 4-bromocrotonic acid)	---	1.13 ± 0.15	0.00
10 4-bromocrotonic acid	0.03	0.06 ± 0.06	95 ± 5

TABLE IIIInhibition of Carnitine palmitoyltransferase I (CPT I)*

	Inhibitor	pmol product /mg protein	% inhibition
15	control	0.75	0
	glybenclamide (5 mM)	0.00	100
	malonyl CoA (5 mM)	0.59	22
	tolbutamide (5 mM)	0.07	90
	2-bromopalmitic acid (5 mM)	0.07	91
20	perhexiline (5 mM)	0.10	86

*The CPT-I assay method-I was used for these analyses.

TABLE IVInhibition of Carnitine palmitoyltransferase I (CPT I)

	Inhibitor	pmol product/mg protein	% inhibition
25	control (oxfenicine)	1.15	0
	oxfenicine (1 mM)	0.64	44
	control (for methyl palmoxirate)	0.6	0
	methyl palmoxirate (50 mM)	0.146	92.3

The CPT-I assay method-II was used for these analyses.

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TABLE VInhibition of acyl-CoA dehydrogenase by methylenecyclopropylacetic acid

	Inhibitor	nmol product/mg protein	% inhibition
	control	1.62	0
35	methylenecyclopropyl-acetic acid (MCPA) (1 mM)	0.497	69.3

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TABLE VI

Inhibition of 3-ketoacyl-CoA thiolase by 4-bromocrotonic acid

	Inhibitor	nmol product/mg protein	% inhibition
	control	0.87	0
5	4-bromocrotonic acid (0.5 mM)	0.128	85.2

TABLE VII

Inhibition of human hair follicle growth by an inhibitor of fatty acid synthetase

	Inhibitor	Dose (TM)	Hair follicle length increase (mm)	% Inhibition
	control	---	1.04 ± 0.22	0
10	cerulenin	10	0.06 ± 0.05	93.7 ± 5.6

TABLE VIII

Inhibition of hamster hair mass by an inhibitor of stearoyl-CoA desaturase

	Compound	Dose (%)	Vehicle	Treated (mg)	Control (mg)	% Inhibition
	methyl sterulate	2.5	E*	1.4±0.2	2.65±0.3	45.1 ± 6.8
15	*Vehicles: E -- 90% ethanol, 10% polyethylene glycol.					

TABLE IX

Inhibition of human hair follicle growth by an inhibitor of stearoyl-CoA desaturase

	Inhibitor	Dose	Hair follicle length (increase mm)	% Inhibition
	control	---	1.45 ± 0.52	0
20	methyl sterulate	1 mM	0.59 ± 0.29	59.3 ± 0.2

Other embodiments are within the claims.

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CLAIMS

1. A method of reducing mammalian hair growth which comprises:
selecting an area of skin from which reduced hair growth is desired; and
applying to said area of skin a dermatologically acceptable composition
5 comprising a compound that inhibits fatty acid metabolism.
2. The method of claim 1, wherein said compound is an inhibitor of an
enzyme involved in fatty acid metabolism.
3. The method of claim 1, wherein said compound inhibits fatty acid
oxidation.
- 10 4. The method of claim 3, wherein said compound is an inhibitor of an
enzyme involved in fatty acid oxidation.
5. The method of claim 4, wherein said enzyme is carnitine
palmitoyltransferase I.
6. The method of claim 5, wherein said inhibitor is selected from
15 adriamycin; D,L-aminocarnitine; decanoylcarnitine; amiodarone; 2-bromopalmitic acid;
2-bromopalmitoylcarnitine; 2-bromopalmitoyl-CoA; 2-bromomyristoylthiocarnitine;
emeriamine; erucic acid; erucylcarnitine; etomoxir; etomoxiryl-CoA; glyburide;
hemiacetylcarnitinium chloride; hemipalmitoylcarnitinium chloride; 3-hydroxy-5-5-
dimethylhexanoic acid; methyl palmoxirate; 2-tetradecylglycidic acid; oxfenicine;
20 perhexiline; 2[5(4-chlorophenyl) pentyl]-oxirane-2-carboxylic acid; 2-[3-(3-
trifluoromethylphenyl)-propyl]oxiran-2-carbonyl-CoA; 2-[5-(4-chlorophenyl)pentyl]-
oxiran-2-carbonyl-CoA; 2-(5-phenylpentyl)oxiran-2-carbonyl-CoA; 2-tetradecyloxiran-2-
carbonyl-CoA; 8,N,N-diethylamino-octyl-3,4,5-trimethoxybenzoate; tolbutamide;
trimetazidine.
- 25 7. The method of claim 4, wherein said enzyme is carnitine
palmitoyltransferase II.
8. The method of claim 4 wherein said enzyme is acyl-CoA dehydrogenase.
9. The method of claim 8 wherein said inhibitor is selected from hypoglycin;
2-mercaptoacetic acid; 3-mercaptopropionic acid; methylenecyclopropylacetic acid;
30 methylenecyclopropylformic acid; spiropentaneacetic acid; 3-methyleneoctanoyl-CoA; 3-
methyl-trans-2-octenoyl-CoA.
10. The method of claim 4, wherein said enzyme is enoyl-CoA hydratase.
11. The method of claim 4, wherein said enzyme is L-3-hydroxyl-acyl-CoA

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- dehydrogenase.
12. The method of claim 4, wherein said enzyme is 3-ketoacyl-CoA thiolase.
13. The method of claim 12, wherein said inhibitor is selected from 4-bromocrotonic acid; 2-bromooctanoic acid; 2-bromo-3-ketoctanoyl-CoA; 4-bromo-2-octenoic acid; 4-pentenoic acid.
14. The method of claim 1, wherein said compound inhibits fatty acid synthesis.
15. The method of claim 1, wherein said compound is an inhibitor of an enzyme involved in fatty acid synthesis.
16. The method of claim 15, wherein said enzyme is acetyl-CoA carboxylase.
17. The method of claim 16, wherein said inhibitor is selected from 5-(tetradecyloxy)-2-furoic acid; sethoxydim; β,β' -tetramethyl substituted hexadecanedioic acid; 2-n-pentadecyl-benzimidazole-5-carboxylate; 2-methyl-2-(p-(1,2,3,4-tetrahydronaphthyl)phenoxy)propionic acid.
18. The method of claim 15, wherein said enzyme is fatty acid synthetase.
19. The method of claim 18, wherein said inhibitor is selected from cerulenin; carbacerulenin; and 3-carboxy-4-alkyl-2-methylenebutyrolactone.
20. The method of claim 15, wherein said enzyme is stearoyl-CoA desaturase.
21. The method of claim 20, wherein said inhibitor is sterculic acid.
22. The method of any of the preceding claims wherein the concentration of said compound in said composition is between 0.1% and 30%.
23. The method of any of claims 1 to 21, wherein the composition provides a reduction in hair growth of at least 15% when tested in the Golden Syrian Hamster assay.
24. The method of claims 1 to 21, wherein the composition provides a reduction in hair growth of at least 35% when tested in the Golden Syrian Hamster assay.
25. The method of any of claims 1 to 21, wherein the compound is applied to the skin in an amount of from 10 to 3000 micrograms of said compound per square centimeter of skin.
26. The method of any of claims 1 to 21, wherein said mammal is a human.
27. The method of claim 26, wherein said area of skin is on the face of a human.
28. The method of claim 27, wherein the composition is applied to the area of skin in conjunction with shaving.

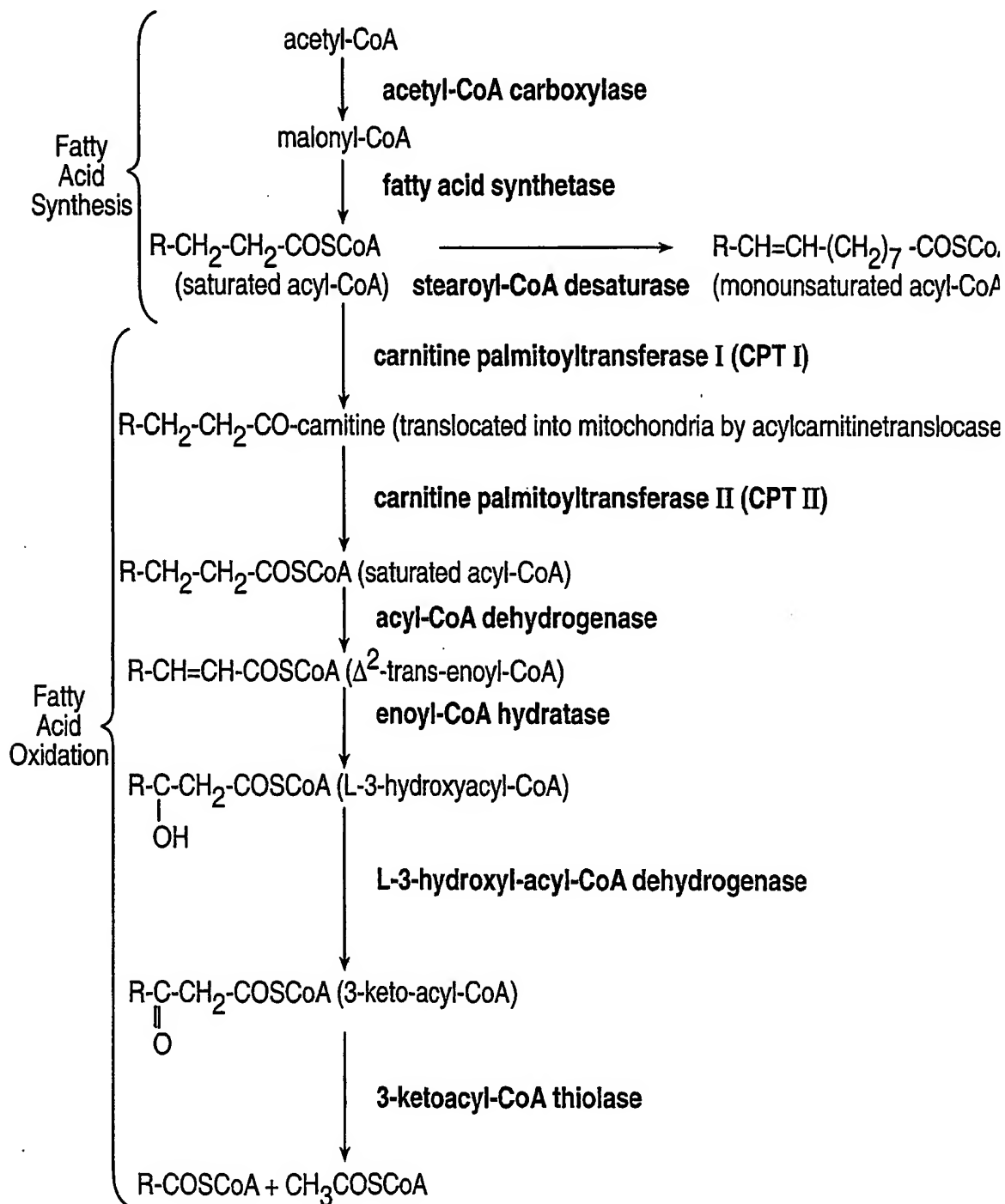
- 18 -

29. The method of claim 26, wherein said area of skin is on a leg of the human.
30. The method of claim 26, wherein said area of skin is on an arm of the human.
- 5 31. The method of claim 26, wherein said area of skin is in an armpit of the human.
32. The method of claim 26, wherein said area of skin is on the torso of the human.
33. The method of any of claims 1 to 21, wherein the composition is applied
10 to an area of skin of a woman with hirsutism.
34. The method of any of claims 1 to 21, wherein said hair growth comprises androgen stimulated hair growth.
35. The method of any of claims 1 to 21, wherein the composition further includes a second compound that also causes a reduction in hair growth.
- 15 36. The method of claim 4, wherein said enzyme is acylcarnitine translocase.
37. The method of claim 3, wherein said compound is 2-propylpentanoic acid.
38. The method of any of claims 1 to 21 wherein said method is a cosmetic method.
39. Use of a compound which inhibits fatty acid mechanism in production of
20 a medicament for reducing hair growth.
40. A composition for reducing unwanted hair growth which comprises a compound that inhibits fatty acid mechanism.
41. Use of a composition comprising a compound that inhibits fatty acid mechanism for reducing unwanted hair growth.

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Figure

Fatty acid metabolism pathway



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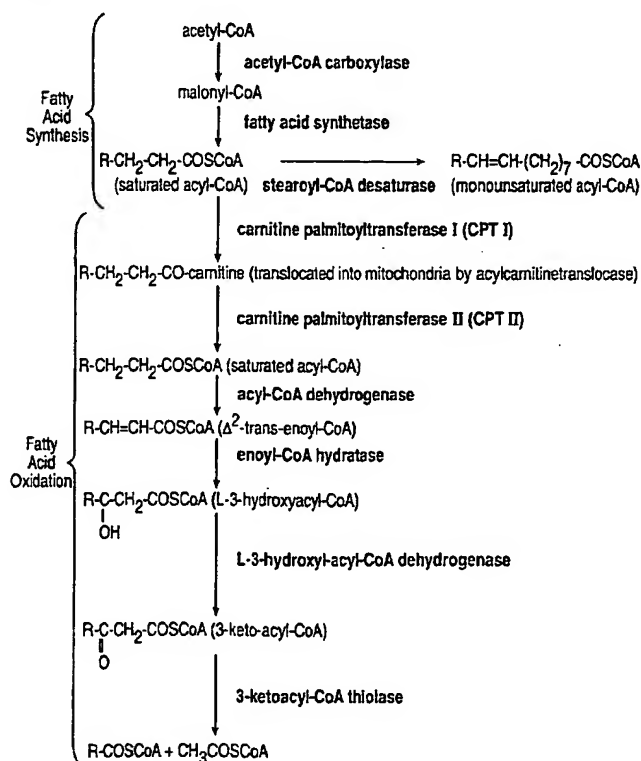
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- (71) Applicant (for all designated States except US): **THE GILLETTE COMPANY** [US/US]; Prudential Tower Building, Boston, MA 02199 (US).
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[Continued on next page]

(54) Title: REDUCTION OF HAIR GROWTH

Fatty acid metabolism pathway



(57) Abstract: Mammalian hair growth can be reduced by topical application of an inhibitor of fatty acid metabolism.

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INTERNATIONAL SEARCH REPORT

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Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 872 248 A (ACCESS PHARMA INC) 21 October 1998 (1998-10-21) claims 1,15	40
A	US 5 362 748 A (SCHWEN RICHARD J ET AL) 8 November 1994 (1994-11-08) claims 1-8	1-6, 23-35, 37-41
A	EP 0 943 311 A (KAO CORP) 22 September 1999 (1999-09-22) claims 1-5; examples 1-4	1-6, 23-35, 37-41
A	WO 95 33439 A (PROCTER & GAMBLE) 14 December 1995 (1995-12-14) page 2, line 8-16; claims 1-10	1-6, 23-35, 37-41
	--- -/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>PATENT ABSTRACTS OF JAPAN vol. 2000, no. 16, 8 May 2001 (2001-05-08) & JP 2001 026522 A (KAO CORP), 30 January 2001 (2001-01-30) abstract</p> <hr/>	<p>1-6, 23-35, 37-41</p>

INTERNATIONAL SEARCH REPORT

International application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: -see box 3
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
Although claims 1-38 and 41 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-4(part), 5-6,23-35(part), 37, 38-41(part)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.1

Although claims 1-38 and 41 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: -see box 3

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

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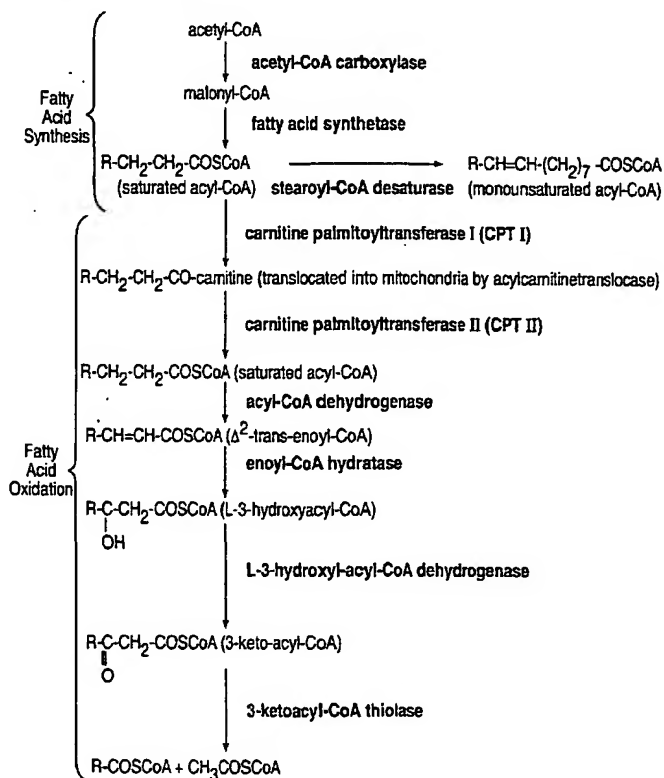
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(54) Title: REDUCTION OF HAIR GROWTH

Fatty acid metabolism pathway



(57) Abstract: Mammalian hair growth can be reduced by topical application of an inhibitor of fatty acid metabolism.



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CLAIMS

1. A method of reducing mammalian hair growth which comprises:
selecting an area of skin from which reduced hair growth is desired; and
applying to said area of skin a dermatologically acceptable composition
5 comprising a compound other than adriamycin that inhibits fatty acid metabolism.
2. The method of claim 1, wherein said compound is an inhibitor of an enzyme involved in fatty acid metabolism.
3. The method of claim 1, wherein said compound inhibits fatty acid oxidation.
- 10 4. The method of claim 3, wherein said compound is an inhibitor of an enzyme involved in fatty acid oxidation.
5. The method of claim 4, wherein said enzyme is carnitine palmitoyltransferase I.
6. The method of claim 5, wherein said inhibitor is selected from
15 adriamycin; D,L-aminocarnitine; decanoylcarnitine; amiodarone; 2-bromopalmitic acid; 2-bromopalmitoylcarnitine; 2-bromopalmitoyl-CoA; 2-bromomyristoylthiocarnitine; emeramine; erucic acid; eracylcarnitine; etomoxir; etomoxiryl-CoA; glyburide; hemiacetylcarnitinium chloride; hemipalmitoylcarnitinium chloride; 3-hydroxy-5-5-dimethylhexanoic acid; methyl palmoxirate; 2-tetradecylglycidic acid; oxfenicine;
20 perhexiline; 2[5(4-chlorophenyl) pentyl]-oxirane-2-carboxylic acid; 2-[3-(3-trifluoromethylphenyl)-propyl]oxiran-2-carbonyl-CoA; 2-[5-(4-chlorophenyl)pentyl]-oxiran-2-carbonyl-CoA; 2-(5-phenylpentyl)oxiran-2-carbonyl-CoA; 2-tetradecyloxiran-2-carbonyl-CoA; 8,N,N-diethylamino-octyl-3,4,5-trimethoxybenzoate; tolbutamide; trimetazidine.
- 25 7. The method of claim 4, wherein said enzyme is carnitine palmitoyltransferase II.
8. The method of claim 4 wherein said enzyme is acyl-CoA dehydrogenase.
9. The method of claim 8 wherein said inhibitor is selected from hypoglycin; 2-mercaptoacetic acid; 3-mercaptopropionic acid; methylenecyclopropylacetic acid;
30 methylenecyclopropylformic acid; spiropentaneacetic acid; 3-methyleneoctanoyl-CoA; 3-methyl-trans-2-octenoyl-CoA.
10. The method of claim 4, wherein said enzyme is enoyl-CoA hydratase.
11. The method of claim 4, wherein said enzyme is L-3-hydroxyl-acyl-CoA

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